REMARKS

Claims 1-3, 7, 10, and 12-14 have been canceled herein. Such cancellation is without prejudice on the merits to further prosecution of these claims in one or more continuing applications.

Claims 4, 6, and 11 have been amended herein. Claims 4-6, 8, and 9 are currently active. Favorable reconsideration is respectfully requested.

Claim 11 remains in the application, but has been withdrawn pursuant to the earlier restriction requirement, now made final. In accordance with the holdings *In re Brouwer*, 37 USPQ2d 1663 and *In Re Ochial*, 37 USPQ2d 1127, Applicants have left Claim 11 pending and amended Claim 11 (a method claim) to depend from Claim 3 (a product claim). In the event Claim 3 is found to contain allowable subject matter, Applicants intend to rejoin Claim 11.

Objections to the Specification:

The status of the various patent applications cited in the application as filed have been updated. The recitation of application Serial No. 09/592,769 (at page 21) was a typographical error. Applicants intended to recite application Serial No. 09/592,756, as presented at page 16 of the application as filed. The corresponding passage at page 21 has been updated in the present amendment to refer to U.S. Patent No. 6,727,368 (the patent that issued from Serial No. 09/592,756).

Objections to Claims 4 and 6:

The objections to Claims 4 and 6 have been addressed, in part, by amending the Markush terminology of the claims, in accordance with the Examiner's recommendation.

The objection is traversed, in part, because the phrase "and salts thereof" is an exceedingly common and unambiguous phrase. The Office has objected to this phrase on the basis that the claims could be misinterpreted to encompass a composition of the compounds and salts together. Applicants do not see how this misinterpretation could arise. The claims do not refer to a "composition," nor do they refer to a "combination."

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Applicants also respectfully note that a salt is a compound. Thus, the claims are clearly directed to the recited compounds and salt forms of those compounds.

Applicants also note that the phrase closes with the word "thereof." The word "thereof" means "of that" or "of it." See Exhibit A, attached hereto and incorporated herein, which is the relevant definition from Webster's Ninth New Collegiate Dictionary. In short, the phrase "and salts thereof" literally and unambiguously refers to salts of the previously recited compounds. In short, the body of these two claims recite compounds that can appear in free form or in the form of a salt. In this regard, please see the specification at page 18, in the paragraph starting at line 19 (which discusses salts of the claimed compounds). Thus, to keep the claims to a manageable length, the free forms of the compounds have been explicitly recited, along with the closing phrase "and salts thereof," to clearly set forth that which the Applicants consider their invention: the free forms of the compounds and the salt forms of the compounds.

Lastly, while Applicants' undersigned counsel is fully aware that comparisons between applications is generally discouraged, it must be noted on the record that the phrase "salts thereof" is exceedingly common within the claims of issued patents. Searching the phrase -- ACLM/"salts thereof" -- within the USPTO's publicly-accessible database yields over 57,000 hits of the phrase "salts thereof" within the claims of issued patents. See Exhibit B, attached hereto and incorporated herein.

Applicants therefore submit that the phrase "and salts thereof" is not reasonably capable of being misinterpreted in the fashion noted by the Office. Withdrawal of this portion of the objection is respectfully requested.

Rejection of Claims 4-6, 8, 9, 12 and 14 Under 35 USC §101 and §112, First Paragraph (Utility/Enablement):

Because these two rejections are very closely related, they shall be addressed simultaneously. (Note that the Office has taken the position, at the bottom of page 8 of the Office Action, that because of the rejection under §101, the claims also stand rejected as

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lacking enablement under §112, first paragraph. The Office has not set forth any additional grounds in support of the rejection under §112, first paragraph.)

As applied to Claims 12 and 14, this rejection has been obviated by cancellation of the claims.

As applied to the remaining claims, these two rejections are respectfully traversed because: (1) the specification as filed establishes a clear, specific, substantial, and credible utility; (2) the art also recognize a specific and substantial utility for non-natural peptide mimetics such as those recited in the present claims; and (3) the Office has not established by way of scientific reasoning or examples why it doubts Applicants' asserted utility for the claimed compounds. Addressing these three points in order:

All of the compounds recited in the present claims contain at least two cyclically-constrained β- and/or γ-amino acid residues. These compounds will not adopt the same conformations as naturally-occurring α-polypeptides because they are constrained in a fashion not found in naturally-occurring polypeptides. Nor are the conformations adopted by the present compounds exhibited by all compounds or all proteins/polypeptides in general. To be scrupulously precise, the presently claimed compounds will adopt a more limited number of conformations than the analogous α-polypeptides. This is due to the rotational constraints imposed by placing the backbone carbon atoms into a cyclic moiety. That being said, because the present compounds are composed of peptide bonds, the present compounds do adopt conformations that mimic those of natural polypeptides and proteins. See the cited passage below from page 24 of the present specification. See also the paragraph at page 24, line 25 of the specification as filed "Thus, the present inventors have shown that the γ-peptides **1**, **2**, and **3** adopt sheet secondary structure in solution." The cyclically-constrained amino-acid residues positively required by the present claims are non-natural and constrained in a fashion distinctly different and more limited than natural polypeptides. In short, the claimed compounds have fewer degrees of freedom as compared to naturally-occurring polypeptides composed of α-amino acids (due to placing the backbone carbon atoms into a ring).

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Addressing point (1), Applicants respond that the specification does disclose a credible, specific, and practical utility that is not shared by all compounds. See the passage spanning page 19, line 19, to page 20, line 25:

> The subject compounds find use as peptide mimetics that are not easily degraded by the action of proteolytic enzymes. Thus, the cyclically-constrained peptides of the present invention can be used as probes to explore protein-protein interactions. Because the compounds of the present invention are cyclically-constrained, they are more restricted conformationally than their strictly α-polypeptide counterparts. The compounds can be labeled and tracked throughout any given reaction. The effect the compound has on any given reaction provides valuable information on either or both of the kinetics and/or thermodynamics of the reaction being studied. Such reactions can be performed *in vitro*, *in vivo*, and *ex vivo*.
>
> Libraries of the subject compounds can also be prepared by automated means, thus providing access to a huge database which can be used as a tool to test, for example, potentially biologically-active agents.
>
> One highly useful aspect of the invention is that because the backbone is heterogenous, a portion of the residues, such as the α-amino acids, provide functional diversity (thus allowing many different types of reactions in many different types of environments to be explored), while the cyclically-constrained residues provide conformational specificity and stability. For example, massive diversity can be obtained using commercially-available α-amino acids as building blocks, while structural rigidity is conferred by using only a single type of rigidified (*i.e.*, cyclically-constrained) β- or γ-amino acid.
>
> With particular focus on protein-protein interactions, it has long been a goal of biological scientists to disrupt specific protein-protein interactions as a means to explore the nature of the interaction. This goal has proven difficult to achieve using traditional small molecules. Binding size is likely part of the problem. Protein-protein complexes generally involve relatively large molecular surfaces. This makes it difficult for a small molecule to bind competitively at such a site. The present compounds, however, are polyamides and can be quite large. Thus, as a class, these compounds, individually and in the form of large libraries of compounds, are much better suited for probing protein-protein interactions than are small molecules. Additionally, the conformations of the subject compounds are periodic; the conformations can be extended simply by adding additional monomers to the polypeptide. Thus, the present compounds can be fabricated as relatively small skeletons or as very large skeletons, the size being dictated, at least in part, by the size of the binding site to be studied.

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See also the passage bridging pages 24-25 of the specification:

> The utility of these compounds for probing protein interactions is great because, as noted above, the γ-peptides adopt structures analogous to those seen in natural proteins and peptides. Thus, the subject compounds mimic natural protein conformations in solution, but are resistant or immune to proteolytic degradation by proteases and peptidases. The cyclically-constrained γ-amino acid residues incorporated into homogeneous γ-peptide backbones are useful probes in the study of chemical and enzymatic interactions involving natural proteins. Also, the compounds disclosed herein add greatly to the γ-peptide field, in terms of both the number of alternative secondary structures that can be accessed and the intrinsic stability of those secondary structures. The subject compounds are useful probes because the cyclically- constrained residues create secondary structures with high conformational stability at short oligomer lengths that are also resistant to enzymatic degradation. The invention thus enhances the control over γ-peptide folding preferences, thereby providing a larger "toolbox" of probes to be used in investigating the function of naturally-occurring proteins.

Modeling of biological systems using peptidomimetic compounds is unquestionably a very useful endeavor. The ability to mimic a naturally-occurring phenomenon, under tightly controlled conditions, is both practical and useful. The stated utility is also directed specifically (perhaps even uniquely) to the present compounds because they are non-natural and structurally rigid. As noted above, because of the cyclical constraints in the backbone, while the present compounds mimic natural proteins, they also adopt a far smaller set of conformations. Thus, by using the present compounds as probes, experiments can be conducted under more rigorous conditions than if more labile polypeptidic probes were used.

Delving into this point a little further, the *Brenner v. Manson* case, 383 US 519, is instructive because it stands for the proposition that an invention lack patentable utility if it includes only a general assertion of similarities to known compounds that are known to be useful without sufficient corresponding explanation why the claimed compounds are believed to be similary useful. In the present application, Applicants clearly explain *why* the compounds are useful (from p. 25 of the specification):

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> The subject compounds are useful probes because the cyclically- constrained residues create secondary structures with high conformational stability at short oligomer lengths that are also resistant to enzymatic degradation. The invention thus enhances the control over γ-peptide folding preferences, thereby providing a larger "toolbox" of probes to be used in investigating the function of naturally-occurring proteins.

Applicants thus submit that the application as filed sets forth a specific and credible utility for the claimed compounds.

Addressing point (2), the relevant art also establishes a specific and credible utility for compounds related to those now claimed. According to MPEP §2107.01(II), if there is a well-established utility for the claimed invention, Applicants are entitled to provide evidence of that well-established utility and to rely upon it. As evidence of the utility of the claimed compounds, Applicants submit for the Examiner's consideration Seebach et al. (2003) "Design and Synthesis of γ-Dipeptide Derivatives with Submicromolar Affinities for Human Somatostatin Receptors," *Angew. Chem. Int. Ed.*, 42(7):776-778, attached hereto as Exhibit C. This paper was submitted to the publisher on September 25, 2002 (prior the actual filing date of the present application), but after Applicants' earliest claimed priority date (August 26, 2002). Thus, while the Seebach et al. paper is not prior art to the present application, it is closely contemporaneous with the filing of the present application.

The Seebach et al. paper demonstrates that a well-established utility exists in the contemporaneous literature for compounds akin to those presently claimed **and** that that utility is **exactly the same** as the utility articulated in the present application as filed. In short, in the Seebach et al. paper, a non-cyclically-constrained, gamma-amino acid dipeptide was fabricated and tested for its ability to mimic binding interactions between two proteins: (1) the gamma-dipeptide the Seebach et al. fabricated and (2) five different human somatostatin receptors ($hsst_1$, through $hsst_5$). See the very first paragraph of the Seebach et al. paper. The assay Seebach et al. used to gauge this interaction was sufficiently well know in the prior art that the authors did not bother to include even a cursory description of it, but instead cited only to the prior art paper. See Seebach et al.,

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page 777, right-hand column, first full paragraph. Seebach et al. cite to footnote 10, Hannon et al. (2002) Neuropharmacology 42:396-413.

More telling still is that the authors of the Seebach et al. paper did not rationally design the dipeptide they tested. They simply fabricated it from readily available, commercial starting materials. See page 776 the Seebach et al. paper. The discussion at the left-hand column of 777 of Seebach et al. and continuing to the top of the right-hand column, however, indicates that Seebach et al. also found evidence that the compound they tested adopt distinct and stable secondary structure.

Perhaps most telling of all is that Seebach et al. describe their results in positively glowing terms as "confirmative, surprising, and promising." See page 777, right-hand column, second full paragraph. Applicants do not disagree. Seebach et al's work has real-world, practical, credible, and significant utility, in exactly the same fashion as the subject invention. Applicants therefore submit that the are also provides a credible and specific utility for the compounds recited in the claims.

Addressing point (3), the Office has not established by way of scientific reasoning or examples why it doubts Applicants' asserted utility for the claimed compounds. The Seebach et al. paper clearly established a recognized utility for compounds of the type claimed. The quotes provided by the Office at the top of page 8 of the Office Action appear to bolster Applicants' position, rather than refute it. The quotes supplied by the Office indicate that compounds of the type now claimed have "practical significance," and that the compounds "provide useful scaffolds for creation of biologically active molecules with predetermined shapes." Rather than suggesting that the present compounds lack a specific and credible utility, these quotes clearly indicate that compounds now claimed are quite useful as peptidomimetics - a very specific, credible, and practical utility.

Applicants therefore submit that the rejection of the claims under §101 and §112, first paragraph (enablement) is improper. Withdrawal of the rejection is respectfully requested.

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Rejection of Claims 4-6, 8, 9, 12 and 14 Under 35 USC §112, First Paragraph (Written Description):

As applied to Claims 12 and 14, this rejection has been obviated by appropriate amendment to the claims. As applied to Claims 4-6, 8, and 9, this rejection is respectfully traversed.

Applicants respectfully note that many of the parameters noted by the Office in the paragraphs spanning pages 9-11 of the Office Action are not relevant to the present claims because the present claims do not encompass "biomolecules." Specifically, the citations to *Fiers v. Sugano* and *The Regents of University of California v. Eli Lilly & Co.* in support of this rejection (at page 9 of the Office Action) are inapposite. Notably, the quote from *Fiers* that:

> Disclosure sufficient to satisfy the written description requirement... must include a precise definition of DNA, such as by structure, formula, chemical name, or physical properties (emphasis added),

is contained in dictum and was not the holding of the court. Consequently, the above quote from *Fiers* is not a controlling statement on the written description requirement. (Note also that the string of requirements is in the alternative.) Contrary to Judge Lourie's above-quoted dictum from *Fiers*, it has never been the law that an Applicant must know the structure of a compound (DNA, protein, or otherwise) in order to satisfy the written description requirements of §112, first paragraph.

The controlling law in this instance is provided by *In re Fisher*, 166 USPQ 18 (CCPA 1970). In *Fisher*, the question was whether the claims of a CIP application (drawn to a protein) were entitled to the filing date of the parent application. In *Fisher*, it was undisputed that the amino acid sequence of the protein claimed in the CIP was not disclosed in the parent application, and further that *Fisher* did not know the amino acid sequence at the time the parent application was filed (166 USPQ at 21). The only disclosure in the parent application was a process for extracting the protein from the pituitary glands of certain animals. However, an article which appeared after the filing of the CIP application confirmed that the claimed sequence was, in fact, the sequence of

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protein described in the parent application. The CCPA held that the claimed structure was inherent in the description contained in the parent application, and therefore the parent application described the protein to the level required by §112, first paragraph.

Additionally, the discussion at the bottom of page 9 and extending to the top of page 10 of the Office Action regarding "biomolecules" that are described only by functional characteristics and a method of obtaining a claimed sequence is irrelevant because that discussion from MPEP 2163 clearly applies to naturally-occurring molecules isolated from nature, such as cDNAs and the like. The relevant and complete quote from MPEP 2163 reads as follows:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA.

The presently compounds have no corresponding biological function; they have no corresponding "genetic code." The presently claimed compounds are not products of nature. They are not "biomolecules" as that term is used in MPEP 2163. Rather, the claimed compounds are "unnatural polypeptide compounds," as is positively recited in the preambles to Claims 4 and 6. Thus, the above-quoted passage from MPEP 2163 is inapposite to the present claims.

In contrast to the case law noted by the Office, Applicants respectfully note that "compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Enzo Biochem, Inc.*, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002). With specific regard to compounds (and because of the fact-intensive nature of the written description inquiry)

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Applicants are also free to describe compounds by "whatever characteristics sufficiently distinguish [them]" See *Amgen, Inc. v. Chugai Pharmaceutical,* 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

Turning to the specification and claim language, the invention currently claimed is a genus of non-natural polypeptides. They are not products isolated from nature. The are not semi-synthetic. They are entirely unnatural, synthetic, and synthesized de novo using polypeptide chemistry. A rather large selection of the claimed compounds are exemplified in the application as filed. Various routes to synthesize the claimed compounds, using solution-phase and solid-phase peptide chemistries are exhaustively detailed in the application as filed:

Starting at the last paragraph of page 15 of the application as filed, several terms used in the claims are explicitly defined, including the terms "α-amino acid" (p. 15, line 27), "β-amino acid" (p. 16, line 12), "γ-amino acid" (p. 16, line 22), "cyclically-constrained" (p. 16, line 26), "reverse turn moiety" (p. 17, line 4), "amino-terminus protecting group" and "carboxy-terminus protecting group" (p. 17, line 21), and "salts" (p. 18, line 19).

As seen in the updated paragraphs included in this amendment, the specification incorporates by reference several earlier patents to Gellman et al. See page 21 of the specification.

Extending from page 21 to page 30 of the specification is a general discussion of β-amino acids, γ-amino acids, and an overview of how these building blocks are synthesized.

An exhaustively detailed description of the relevant chemistry require to make the claimed compounds begins at the bottom of page 30 of the specification. After introductory remarks about materials and methods (e.g, melting points, IR, NMR, UV, and CD spectroscopy), a detailed description of the preferred method for linking the α-, β-, and γ-amino acid together spans page 32 to page 36 of the specification. A general reaction scheme (Reaction 7) for solid-phase synthesis is provided at page 34; a specific coupling scheme for solution-phase synthesis is provided at page 35.

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A section addressing how to add substituents to the cyclic moieties (including a specific exemplary reaction scheme) is provided at pages 36 to 38.

A still more detailed description of how to couple the amino acids together to yield the compounds as claimed is provided at pages 39-52 of the specification. A discussion about the solution-phase conformations of the claimed compounds is provided at pages 52-55.

Most notably for purposes of the written description requirement, the application as filed contains an extensive series of Examples that begins on page 55 and extends to page 116 of the application as filed. In short, Applicants provided 61 type-written pages of actual working examples of the compounds now claimed. The Examples include solution- and solid-phase synthesis of the claimed compounds, extensive proton and ^{13}C NMR data and MS data for the compounds, and a wealth of additional spectroscopic data on a host of final compounds falling within the scope of the claims. See, for example, the spectra presented in Figs. 5, 6A, and 6B.

All of these compounds share one salient feature: they are non-natural β-amino acid compounds that include a structurally rigid cyclic moiety in their backbone carbon chain. Applicants respectfully submit that this genus of compounds is extensively described in the specification as filed. Thus, Applicants respectfully submit that the rejection of the claims under §112, first paragraph, written description, is improper. Withdrawal of the same is respectfully requested.

Rejection of Claims 4-6, 8, 9, 12 and 14 Under 35 USC §102(b) in View of "Appella-2," (Appella et al. (1999), "Formation of Short, Stable Helices in Aqueous Solution by β-Amino Acid Hexamers," *J. Am. Chem. Soc.* 121:2309-2310):

(N.B.: Applicants' undersigned counsel thanks Examiner Kosar for the very brief, informal telephone conversation held on August 4, 2005. At issue was which "Appella et al." reference the Office was citing in this rejection— there are six "Appella et al." references now of record in the application. Page 8 of the present Office Action identifies

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"Appella-2" as the above-noted reference. The call was placed by Applicants' counsel to confirm that the Office was, in fact, referring to this same reference.)

As applied to Claims 12 and 14, this rejection has been obviated by cancellation of the claims.

As applied to Claims 4-6, 8, and 9, this rejection is respectfully traversed because the structure drawn at page 13 of the Office Action is not disclosed in the Appella et al. paper. The Office accidentally inserted into its figure conventional α-Lys residues, while all of the structures shown in Appella et al. incorporate β-Lys residues. Thus the Appella et al. paper does not disclose any of the compounds positively recited in the present claims.

All of the present claims require that at least one of the X or Z residues comprises an α-amino acid residue. Because the Appella et al. reference does not include any compounds that have an α-amino acid residue, it is respectfully submitted that this rejection is improper.

In particular, see the passage at page 2309 of the Appella et al. paper, right-hand column, end of the first full paragraph:

> We then prepared a series of hexa-β-peptides, 1-4, with varying proportions of cyclohexyl and acyclic β-amino acid residues. The acyclic residues were synthesized from the corresponding D-α-amino acids (ornithine, phenylalanine, or valine) by the elegant Seebach method [citation omitted; emphasis added].

A close examination of compounds 1-4 shown in the Appella et al. paper reveals that the acyclic residues in each of compounds 1-4 is not an α-Lys residue (as shown in the Office's structure at page 13 of the Office Action), but is rather is a β-Lys residue. All of the compounds 1-4 of the Appella et al. paper are β-amino acid hexapeptides. None of compounds 1-4 of Appella et al. include an α-amino acid residue.

For this reason, Applicants respectfully submit that the rejection of Claims 4-6, 8, and 9 over Appella et al. is improper. Withdrawal of the rejection is requested.

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In light of the above amendment and remarks, Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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